UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte BRUCE A. BEUTLER and
ALEXANDER POLTORAK

Appeal No. 2004-2206
Application No. 09/396,985

ON BRIEF

Before WILLIAM F. SMITH, ADAMS, and GRIMES, Administrative Patent Judges.

WILLIAM F. SMITH, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the examiner's rejection of claims 38-40, 52-61, 63-68, 70-75, and 100-103. Claims 38, 39, and 101 are representative of the subject matter on appeal and read as follows:

38. A method of screening for modulators of a lipopolysaccharide mediated response comprising the steps of:

a) obtaining a cell expressing a TLR-4 polypeptide;

b) measuring a lipopolysaccharide mediated response mediated by the TLR-4 polypeptide;

c) contacting the TLR-4 polypeptide with a putative modulator;

d) assaying for a change in the lipopolysaccharide mediated response; and

e) comparing the lipopolysaccharide mediated responses mediated by the TLR-4 polypeptide obtained in steps b) and d) above

wherein a difference in the lipopolysaccharide mediated responses indicates that the putative modulator is a modulator of a lipopolysaccharide mediated response.

39. The method of claim 38, wherein the TLR-4 polypeptide has the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 or SEQ ID NO:99.

101. The method of claim 38, wherein said putative modulator to be screened is a small molecule.

The examiner does not rely upon references in rejecting the claims.

Claims 38-40, 52-61, 63-68, 70-75, and 100-103 stand rejected under 35 U.S.C. § 112, second paragraph. Claims 38-40, 52-61, 63-68, 70-75, and 100-103 also stand rejected under 35 U.S.C. § 112, first paragraph (enablement).

We affirm the rejection under 35 U.S.C. § 112, second paragraph, with respect to claims 38, 52-56, 63-73, 75, and 101-103. We reverse this rejection with respect to claims 39, 40, 57-61, 74, and 100.

We vacate the rejection under 35 U.S.C. § 112, first paragraph (enablement) with respect to claims 38, 52-56, 63-73, 75, and 101-103 and reverse this rejection with respect to claims 39, 40, 57-61, 74, and 100.

Background

Endotoxin recognition is stated to be an early warning signal so that a host may mount a timely defense against invasion by Gram-negative organisms. Specification, page 2. Since widespread activation of macrophages by endotoxin results in

development of septic shock, id., page 3, endotoxin and Gram-negative organisms have been long studied. As explained by appellants:

> Thirty years ago, mice of the C3H/HeJ strain were noted to be specifically and globally unresponsive to endotoxin, while closely related animals of the C3H/HeN or C3H/OuJ substrains exhibited normal response (Sultzer, 1968). The median lethal dose of endotoxin is more than 100-fold higher in C3H/HeJ mice than in either of these other strains. Macrophages of C3H/HeJ mice fail to produce cytokines in response to endotoxin, and B-lymphocytes of C3H/HeJ mice are not driven to proliferate by endotoxin. While C3H/HeJ mice are highly resistant to the lethal effect of endotoxin, they are unusually sensitive to infection by gram-negative organisms. The mean lethal inoculum with Salmonella typhimurium, for example, is two organisms in C3H/HeJ mice, whereas several thousand organisms are required to kill mice of the C3H/HeN strain. Hence, the ability to sense the presence of endotoxin is required for defense against gram-negative organisms and it is speculated that individuals that suffer from sepsis and septic shock have a similar genetic mutation which causes them to be more susceptible to infection.

Specification, page 4.

The defective responses by the C3H/HeJ mice are stated to be the result of a single, codominant mutation. Id. Appellants explain:

> Mice homozygous for the mutant allele of the 'Lps gene' are unresponsive to endotoxin, whereas homozygotes for the common allele are normally responsive whether lethality or cell-based assays are employed as an index. Heterozygotes exhibit intermediate levels of response. The protein encoded by this mutant gene is the most important known determinant of endotoxin-induced TNF biosynthesis, and indeed, of all reactions to endotoxin.

Id.

The present invention involves appellants' discovery that a polypeptide denominated toll-4 or tlr-4 plays a role as the lps receptor and thus is involved in the pathway leading to immune response to certain infections especially those involving

Gram-negative bacteria. Id., page 5. Appellants explain the present invention as follows:

> In broad aspects, the present invention provides methods for screening for susceptibility to infection. On the basis of 2093 meioses analyzed in two separate intraspecific backcrosses, the location of the mouse Lps^{d} mutation has been circumscribed to a genetic interval 0.9 cM in size. To identify gene candidates, nearly 40,000 sequencing runs were performed across the critical region. Selective hybridization and exon trapping were also employed to identify genes throughout the 'zero' region. These studies revealed that only a single intact gene was identified within the entire critical region. This gene encodes the TLR-4 receptor, a member of the IL-1 family of receptors. Thus, the present inventors demonstrate that there is a mutation in the TLR-4-encoding gene that appears to provide a predisposition to infection.

Specification, page 23.

Appellants also state:

> It was found that in the macrophages of mice that are susceptible to bacterial infection there is a genetic mutation in the lps locus. Specifically, there is a mutation in the TLR-4 receptor that is expressed by the macrophages of these compromised mice and this mutation leads to a reduced recognition of endotoxin. As the endotoxin is not recognized by these defense cells, there is a lack of immune response mounted against the invading bacteria which results in the deleterious effect of the infection. The present invention suggest that similar mechanisms work in other mammalian cells and as such in a broad sense the present invention provides methods of preventing a bacterial infection of a host comprising ensuring that the macrophages of the host express a function TLR-4 or Toll-like receptor. By providing such a functional receptor, the present invention ensures that the endotoxin signal is recognized by the immune system of the host. Conversely, in those instances in which widespread activation of macrophages by endotoxin results in the overproduction of TNF leading to the development of septic shock, it may be desirable to down-regulate the TLR-4 receptor.

Specification, paragraph bridging pages 23 and 24.

The claims under review in this appeal are directed to a method of screening for modulators of a lipopolysaccharide (lps) mediated response. Significantly, claim 38

requires a cell expressing a "TLR-4 polypeptide" as well as "assaying for a change in the lipopolysaccharide mediated response."

Discussion

1. Definiteness rejection

Appellants state that with respect to this rejection the claims do not stand or fall together. Appeal Brief, page 3. Appellants indicate that claims 39, 40, 57-61, 74, and 100 are separately patentable. Thus, we shall consider the merits of this rejection based upon two groups of claims, group 1 being claims 38, 52-56, 63-73, 75, and 101-103 and group 2 being claims 39, 40, 57-61, 74, and 100.

(a) Group 1 Claims.

There are three aspects to the examiner's indefiniteness rejection. The examiner first states that "without a clear disclosure and associated function of the TLR-4 protein the metes and bounds of the claim[s] cannot be determined." Examiner's Answer, page 5. The examiner next questions the scope of the phrase "mediation of lipopolysaccharide mediated response." Id. Finally, the examiner considers the use of the term "small molecule" in claims 101-103 to be a relative term which renders the claims indefinite. Id., page 6.

We agree with the examiner in regard to the first stated reason for this rejection with respect to the claims of group 1. Appellants' use of the phrase "TLR-4 polypeptide" renders the claims indefinite as to the metes and bounds of the polypeptide.

As set forth in In re Marosi, 710 F.2d 799, 802, 218 USPQ 289, 292 (Fed. Cir. 1983), "It is well established that 'claims are not to be read in a vacuum, and limitations

therein are to be interpreted in light of the specification in giving them their "broadest reasonable interpretation,"" citing In re Okuzawa, 537 F.2d 545, 548, 190 USPQ 464, 466 (CCPA 1976). Furthermore, we have been cautioned that before a patent application is granted, there is no reason to read into the claims the limitations of the specification. In re Prater, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-551 (CCPA 1969). We also note that when the questioned claim limitation is a compound, it has been held that one skilled in the art must be able to determine whether a given compound is within the scope of the claim under review. Morton Internat'l Inc. v. Cardinal Chem. Co., 5 F.3d 1464, 1470, 28 USPQ2d 1190, 1195 (Fed. Cir. 1993).

Here, reading the phrase "TLR-4 polypeptide" in light of the specification does not provide sufficient guidance to a person of skill in the art as to the metes and bounds of the compounds encompassed by this phrase. Obviously, the nomenclature "TLR-4 polypeptide" does not in and of itself provide guidance to a person of ordinary skill in the art as to the compounds encompassed thereby. While appellants have described at least five amino acid sequences, i.e., SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98, and SEQ ID NO: 99, as being TLR-4 polypeptides, independent claim 38 is not limited to those polypeptides. Compare claim 38 with claim 39.

The specification also indicates that a TLR-4 polypeptide plays a role as the LPS receptor and is involved in the pathway leading to immune responses in response to certain infections. Specification, page 5. However, TLR-4 polypeptides are not the only compound known to mediate lipopolysaccharide response. As set forth in the specification at pages 3-4, the receptor TLR-2 is known to "partially mediate lipopolysaccharide-induced cellular signaling." Thus, the ability to mediate a

lipopolysaccharide response is not a unique indicator that a given compound is a "TLR-4 polypeptide."

Appellants also rely upon a declaration of Dr. David D. Chaplin filed under 37 CFR § 1.132 in response to this rejection. In relevant part, Dr. Chaplin states:

> 7. The examiner has rejected several claims because the examiner believes that the name 'TLR-4' is not definitive of particular proteins. The examiner states that insufficient structural and functional properties have been presented in the specification to allow the proper identification of a TLR-4 protein. I do not find this to be the case.
>
> 8. Contrary to the examiner's position, my reading of the application provides me with at least sufficient structural and functional properties by which to identify a protein as TLR-4 or its homolog. The particular name associated with TLR-4 and its homologs is not determinative of their identity. Rather, its is [sic] their structure, primarily the similarity of the amino acid sequences among members of the TLR-4 family, and their function, primarily their role in mediating responses to endotoxins, that identifies TLR-4 polypeptides.
>
> 9. First, the family of TLR-4 receptors share high sequence similarities in specific domains, identifiable by their shared sequence motifs, as provided by the application. See, for example, pages 110-122.
>
> 10. Second, the domains of TLR-4 have specific functions, as described in the application. Primarily, TLR-4 polypeptides act to signal the presence of LPS. TLR-4 is an essential component of the signaling process and its ability to so signal is one of its defining functions.
>
> 11. Lastly, researchers in the field of LPS signaling are well aware of the remaining members of the toll-like receptor family, generally, and are able to identify TLR-4 and its homologs using the structural and functional features shared by all TLR-4 polypeptides.

As seen, Dr. Chaplin bases his analysis on the fact that the application provides him with "at least sufficient structural and functional properties by which to identify a protein as TLR-4 or its homolog." Chaplin dec., para. 8. However, as set forth above, neither the specific amino acid sequences set forth in the specification as being TLR-4

polypeptides nor their function as mediating responses to endotoxin adequately define the metes and bounds of the TLR-4 polypeptides required by claim 38.

Dr. Chaplin also refers to a so-called family of TLR-4 receptors that are stated to "share high sequence similarities in specific domains identifiable by their shared sequence motifs, as provided by the application. See, for example, pages 110-122." Id., para 9. To the extent Dr. Chaplin refers to pages 110-122 of the specification as describing a family of TLR-4 receptors that share high sequence similarities in specific domains, we point out that claim 38 is not directed to such a family. Rather, claim 38 merely requires the use of a "TLR-4 polypeptide."

On this basis, the rejection of the group 1 claims under 35 U.S.C. § 112, second paragraph, is affirmed.[1]

We disagree with the examiner that the requirement of claim 38 with respect to "lipopolysaccharide mediated response" renders the claims indefinite. The examiner questions "where does the 'lipopolysaccharide mediated response' pathway begin and end...?" Examiner's Answer, page 6.

Appellants have disclosed at least two assays that are useful in defining a lipopolysaccharide response. See specification, pages 87-88 ("Assays for LPS responsiveness"). The two assays are stated to provide "unambiguous discrimination

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[1] While not before us we note that the issues raised by the examiner in this rejection also implicate the written description requirement of 35 U.S.C. § 112, first paragraph. As stated in University of Rochester v. G.D. Searle & Co., 358 F.3d 916, 926, 69 USPQ2d 1886, 1894 (Fed. Cir. 2004), "Regardless whether a compound is claimed per se or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods."

between responders...and nonresponders...." Id., page 88. While there may be other ways to measure a lipopolysaccharide response, absent an explanation from the examiner as to why the assays described in the specification do not serve to identify a lipopolysaccharide response, we do not find the claims to be indefinite for this reason.

This aspect of the examiner's indefiniteness rejection is reversed.

Nor do we agree with the examiner that the term "small molecule" renders claims 101-103 indefinite. The examiner questions when a small molecule "transitions into a medium or big molecule?" Examiner's Answer, page 6.

It is well settled that claims must be read not only in light of the specification, but in light of the prior art. In re Moore, 439 F.2d 1232, 1235, 169 USPQ 236, 238 (CCPA 1971). Here, the examiner has not discussed how the prior art views "small molecule" inhibitors as required by these claims. Thus, the examiner's analysis of this issue is incomplete.

This aspect of the examiner's indefiniteness requirement is reversed.

(b) Group 2 claims

The group 2 claims are limited to TLR-4 polypeptides defined by an amino acid sequence or by a nucleic acid sequence stated to encode a TLR-4 polypeptide. As such, these claims adequately defined a "TLR-4 polypeptide" as required by claim 38. Thus, we reverse the rejection under 35 U.S.C. § 112, second paragraph, in regard to the group 2 claims.

2. Enablement

(a) Group 1 claims

We have held that the group 1 claims are indefinite under 35 U.S.C. § 112, second paragraph. As explained in In re Moore, 439 F.2d 1232, 1235, 169 USPQ 236, 238 (CCPA 1971), "It is premature to consider whether a given claim is enabled until the metes and bounds of the claim can be determined." Thus, it is appropriate that we vacate the enablement rejection of the group 1 claims pending resolution of the issue raised under 35 U.S.C. § 112, second paragraph, on which we affirmed the indefiniteness rejection.

(b) Group 2 claims

The examiner states that the specification enables "a screening method for compounds which modulate a LPS mediated response by inducing the synthesis or altering expression of TLR-4 SEQ ID NOs: 2, 4, 6, 98 and 99 . . .." Examiner's Answer, page 6.

It is unclear why claims 39, 40, 57-61, 74, and 100 are considered to be nonenabled since they are directed to the subject matter the examiner has stated to be enabled. Accordingly, we reverse the enablement rejection as to these claims.

The decision of the examiner is affirmed-in-part, reversed-in-part, and vacated-in-part.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED-IN-PART;REVERSED-IN-PART; and VACATED-IN-PART

William F. Smith
Administrative Patent Judge

Donald E. Adams
Administrative Patent Judge

Eric Grimes
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